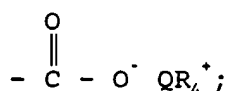




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(21) International Application Number: PCT/US92/09364 (22) International Filing Date: 29 October 1992 (29.10.92) (30) Priority data: 784,267 29 October 1991 (29.10.91) US (60) Parent Application or Grant (63) Related by Continuation US 784,267 (CIP) Filed on 29 October 1991 (29.10.91) (71) Applicant (for all designated States except US): CLOVER CONSOLIDATED, LIMITED [CH/CH]; 37, avenue de Rumini, CH-1002 Lausanne (CH).		(72) Inventors; and (75) Inventors/Applicants (for US only) : SOON-SHIONG, Pa- trick [US/US]; 12307 Dorothy Street, Los Angeles, CA 90049 (US). DESAI, Neil, P. [IN/US]; 847 Alandele Avenue, Los Angeles, CA 90036 (US). SANDFORD, Paul, A. [US/US]; 2822 Overland Avenue, Los Angeles, CA 90064 (US). HEINTZ, Roswitha, A. [US/US]; 1940 Malcolm Avenue, Los Angeles, CA 90025 (US). SO- JOMIHARDJO, Soebianto [ID/US]; 3535 Locksley Drive, Pasadena, CA 91107 (US). (74) Agent: REITER, Stephen, E.; Pretty, Schroeder, Bruegge- mann & Clark, 444 South Flower Street, Suite 2000, Los Angeles, CA 90071 (US). (81) Designated States: AT, AU, BB, BG, BR, CA, CH, CS, DE, DK, ES, FI, GB, HU, JP, KP, KR, LK, LU, MG, MN, MW, NL, NO, PL, RO, RU, SD, SE, US, Euro- pean patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, SN, TD, TG). Published <i>Without international search report and to be republished upon receipt of that report.</i>
(54) Title: CROSSLINKABLE POLYSACCHARIDES, POLYCATIONS AND LIPIDS USEFUL FOR ENCAPSULATION AND DRUG RELEASE (57) Abstract <p>The present invention relates to a new form of biocompatible materials (e.g., lipids, polycations, polysaccharides) which are capable of undergoing free radical polymerization, e.g., by using certain sources of light; methods of modifying certain synthetic and naturally occurring biocompatible materials to make polymerizable microcapsules containing biological material coated with said polymerizable materials, composites of said polymerizable materials, methods of making microcapsules and encapsulating biological materials therein, and apparatus for making microcapsules containing biological cells (particularly islets of Langerhans) coated with polymerizable alginate or with a composite thereof (e.g., alginate and PEG). The present invention also relates to drug delivery systems relating to the foregoing, as well as bioadhesives and wound dressings made utilizing the foregoing technology.</p>		

wherein A is a polysaccharide, polycation, or lipid; X is a moiety containing a carbon-carbon double bond or triple bond capable of free radical polymerization (as described above), A and X are linked covalently as described above,
 5 Y is selected from alkylene glycols, polyalkylene glycols, or hydrophobic onium cations (e.g., tributylammonium iodide, tetrabutylammonium iodide, tetrabutylphosphonium iodide, and the like), and A and Y are linked through any one of the above described covalent linkages. In addition,
 10 where Y is an onium cation, A and Y can be linked through the following ionic bond:



15 wherein Q is nitrogen or phosphorus, and R is hydrogen, an alkyl radical, an aryl radical, an alkaryl radical, or an aralkyl radical.

The process of synthesizing the polymerizable biocompatible material comprises chemically modifying
 20 biocompatible material selected from a lipid, polycation or polysaccharide having a reactive functionality thereon, and then contacting the resulting modified biocompatible material with a free radical initiating system under free radical producing conditions. Reactive functionalities
 25 contemplated include hydroxyl, carboxyl, primary or secondary amine, aldehyde, ketone or ester groups. These groups are required in order to introduce at these sites, the appropriate polymerizable substituent.

Examples of biocompatible materials include
 30 polysaccharides such as alginate, high M-content alginates, polymannuronic acid, polymannuronates, hyaluronic acid, chitosan, chitin, cellulose, starch, glycogen, guar gum, locust bean gum, dextran, levan, inulin, cyclodextran, agarose, xanthan gum, carageenan, heparin, pectin, gellan
 35 gum, scleroglucan, and the like; polycations such as

polyamino acids [e.g., polyhistidine, polylysine, polyornithine, polyarginine, polyalanine-polylysine, poly(histidine, glutamic acid)-polyalanine-polylysine, poly(phenylalanine, glutamic acid)-polyalanine-polylysine, 5 poly(tyrosine, glutamic acid)-polyalanine-polylysine, collagen, gelatin, and the like]; random copolymers of: arginine with tryptophan, tyrosine, or serine; glutamic acid with lysine; glutamic acid with lysine, ornithine, or mixtures thereof; and the like; polymers containing primary 10 amine groups, secondary amine groups, tertiary amine groups or pyridinyl nitrogen(s), such as polyethyleneimine, polyallylamine, polyetheramine, polyvinylpyridine, and the like; and lipids such as phosphatidylethanolamine, phosphatidylserine, phosphatidylinositol, 15 phosphatidylglycerol, dilaurylphosphatidic acid, dipalmitoyl phosphatidyl glycerol, and the like.

A primary requirement of the polymerizable substituent is the presence of moieties containing carbon-carbon double bonds ($C=C$) which are polymerizable with free 20 radicals generated by suitable initiator(s) e.g., an initiator system useful for UV and visible light polymerization. Examples of moieties containing such carbon-carbon double bonds are alkenoic acids (such as acrylic acid, methacrylic acid, and the like), as well as 25 their corresponding acid chlorides (such as acryloyl chloride, methacryloyl chloride, and the like) and corresponding acid anhydrides (such as acrylic anhydride, methacrylic anhydride, and the like), alkenols (such as allyl alcohol, and the like), alkenyl halides (such as 30 allyl chloride, and the like), organometallic alkenyl compounds (such as vinyl magnesium bromide), and the like.

A variety of free radical initiators, as can readily be identified by those of skill in the art, can be employed in the practice of the present invention. Thus, 35 photoinitiators, thermal initiators, and the like, can be